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Determination of protein reduced electrostatic models from smoothed molecular electrostatic potentials

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Introduction

The design of coarse grain (CG) models [1] and their corresponding potential functions [2] for protein computational studies is currently an active field of research, especially in solving long-scale dynamics problems such as protein folding, protein-protein docking, ... For example, to eliminate fast degrees of freedom, it has been shown that one can rely on CG representations only, or on mixtures of CG and more detailed descriptions [3,4] in order to significantly increase the time step in molecular dynamics (MD) simulations. Among the parameters involved in CG potentials, the electrostatic interactions are of major importance [5] since they govern local and global properties such as their stability [6], their flexibility [7], ...

In this poster, we present an approach to design and evaluate reduced point charge models obtained from smoothed molecular electrostatic potentials (MEP). In a previous approach [8], electron density (ED)-based "CG" were determined through a merging/clustering procedure of atom trajectories generated in progressively smoothed ED distribution functions. In the present work, atoms are clustered according to their trajectories defined in a smoothed MEP function, more particularly the Amber potential reported in [9]. A fitting algorithm is applied to evaluate "CG" charges.

1. Location of "CG" points

A hierarchical merging algorithm, based on the idea of Leung *et al.* [10], is used to locate local maxima and minima in a MEP function V_i as a function of the degree of smoothing t .

1. At scale $t = 0$, each atom of a molecular structure is considered as a local maximum or minimum of V . All atoms are thus considered as the starting points of the merging procedure.

2. As t increases from 0.0 to a given maximal value, each point moves continuously along a gradient path to reach a location in the 3D space where: $\vec{\nabla} V(t) = 0$

On a practical point of view, this consists in following the trajectory of the points within the MEP function calculated at t according to Equation:

$$\vec{r}_{V(t)} = \vec{r}_{V(t-\Delta t)} + \frac{\Delta}{V(t)} \vec{\nabla} V(t)$$

2. Molecular electrostatic potential

$$V_A(\vec{r}) = \sum_{a \in A} \frac{Z_a}{|\vec{r} - \vec{R}_a|} \quad \text{Unsmoothed}$$

$$V_{A,t}(\vec{r}) = \sum_{a \in A} \frac{Z_a}{|\vec{r} - \vec{R}_a|} \text{erf}\left(\frac{|\vec{r} - \vec{R}_a|}{2\sqrt{t}}\right) \quad \text{Smoothed [11]}$$

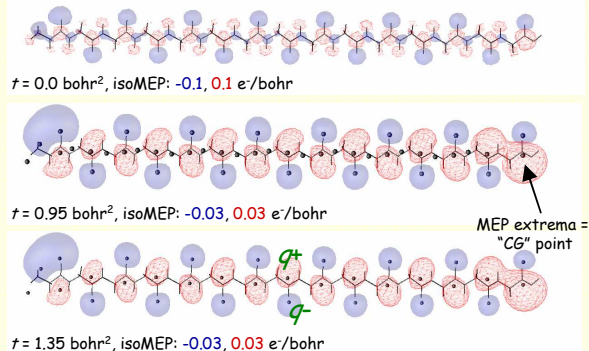
3. Determination of CG charges

This is achieved through the program QFIT [12] to get "CG" point charges fitted from an unsmoothed MEP grid, considering the following constraints: the total molecular charge and dipole.

4. Determination of backbone "CG" charges

a) Construction of Gly₁₅ in an extended conformation ($\Omega = 180^\circ$, $\Phi = -139^\circ$, $\Psi = 135^\circ$) using SMMP05 [13], a Monte Carlo/Simulated Annealing program.

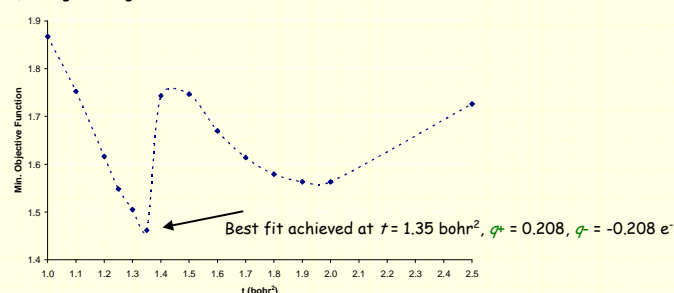
b) Application of the hierarchical merging/clustering algorithm



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c) Charge fitting vs. unsmoothed MEP as a function of t :



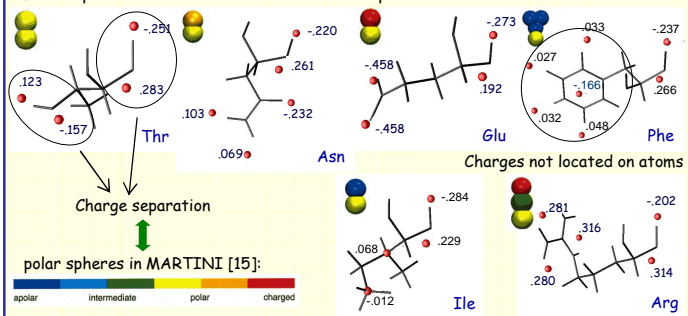
5. Determination of "CG" charges of amino acid side chains

a) Construction of Gly₇-AA-Gly₇ in an extended conformation ($\Omega = 180^\circ$, $\Phi = -139^\circ$, $\Psi = 135^\circ$) with various AA rotamers [14] using SMMP05 [13]. Examples:

	Conformation	$\chi^1 (^\circ)$	$\chi^2 (^\circ)$	$\chi^3 (^\circ)$	$\chi^4 (^\circ)$	Occurrence (%)
Arg	g-, t, g-, g-	300	180	300	300	9.5
	g-, t, g-, t	300	180	300	180	11.9
	g-, t, g+, t	300	180	60	180	12.2
	g-, t, t, t	300	180	180	180	12.2
Asn	t, Nt	180	0			11.1
	t, Og-	180	300			21.3
	t, Og+	180	60			23.6

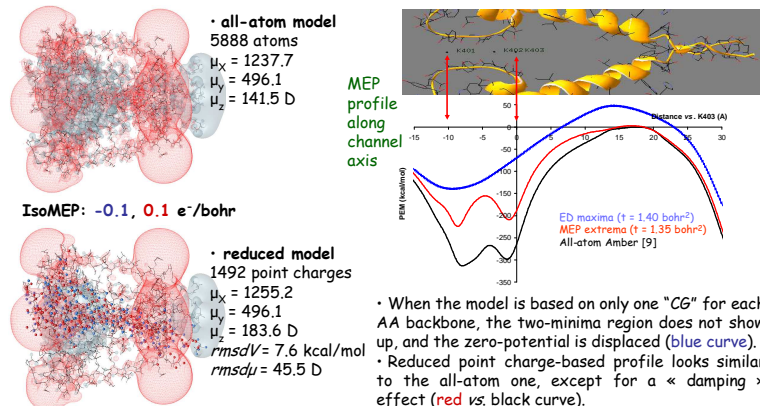
b) Use of "CG" points obtained at $t = 1.35 \text{ bohr}^2$ (see sections 1 and 2)

c) "CG" charge fitting with additional constraints: Gly₁₅ charges (see section 3) except for the points located on the central AA. Examples:



6. Application to potassium ion channel KcsA (1bl8.pdb)

- Positioning of "CG" points through QUATFIT, a superposition algorithm [16], using the above templates and the PDB structure of KcsA
- Extra (+) and (-) charges on terminal N and O \rightarrow 1492-point model (total charge = +4 e⁻)



7. Conclusions, on-going work

- A "CG" model built from a smoothed MEP
- seems to be a more significant electrostatic model than a description based on AA centers-of-mass, for simulating electrostatic effects close to the protein \rightarrow a more complete CG model would involve distinct steric and electrostatic centers
- can be derived for any set of point charges (Amber99, Gromos43A1 also set)
- Transferability has to be confirmed (in progress)
- Easy interfacing with APBS [17], a Poisson-Boltzmann equation solver (tests in progress)